Iranian Journal of Veterinary Science and Technology

Received:2022- Nov- 06
Accepted after revision:2023- May- 20
Published online:2023- May- 20

REVIEW ARTICLE

DOI: 10.22067/ijvst.2023.79476.1203

Role of Various Neurotransmitters in the Central Regulation of Food Intake in the Dorsomedial Nucleus of the Hypothalamus

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ABSTRACT

In living organisms, the central control of nutrition is a highly complex and vital mechanism. Central control of nutrition occurs in various regions of the brain, with the hypothalamus being the most important of which is the hypothalamus. The hypothalamus controls feeding behaviors through neural circuits, specialized nuclei, and central neurotransmitters. Different hypothalamic nuclei involved in regulating food intake include ARC, PVN, LHA, VMH, and DMH. The DMH influences feeding behavior by modulating the activity of different neurotransmitters in the brain. This nucleus receives both orexigenic and anorexic inputs through neural connections with the ARC and other regions of the brain. Due to its location in the brain, the ARC has access to nutritional inputs from the circulation. Within this nucleus, there exist two distinct neuronal populations, namely NPY and POMC. Different inputs from circulation affect two neuronal populations in the ARC. These inputs are related to second-order neurons, including DMH. The DMH integrates these inputs and sends the final output to PVN and LHA. Therefore, DMH affects the central control of feeding regulation through these neural pathways.

Keywords

Feeding, Hypothalamus, Dorsomedial nucleus, Brain neurotransmitters, Orexigenic, Anorexigenic

Number of Figures: 1
Number of Tables: 2
Number of References:: 81
Number of Pages: 10

Abbreviations

CNS: Central Nervous System
ARC: Arcuate nucleus
VMH: Ventromedial hypothalamus
PVN: Paraventricular
LHA: Lateral hypothalamus area
DMH: Dorsomedial hypothalamus

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Introduction

The ability to maintain a balance between energy intake and consumption is very important in living things. Researchers have conducted many types of research on this subject [1]. It has been shown that CNS plays a key role in controlling this balance [2]. Research conducted on CNS includes brain neuroanatomical constructions, peripheral and central hormonal and metabolic signals, as well as examining cellular and molecular pathways [3]. Among different brain regions, the hypothalamus plays an important role in controlling the mentioned pathways [4].

Numerous neurotransmitters and neuropeptides affect the central control of feeding via the hypothalamus. This region plays a crucial role in monitoring basic behavior patterns, particularly feeding behavior [5]. Different types of stimulating and inhibitory peptides generated in the CNS affect feeding (Figure 1) [6]. The central regulation of feeding behavior and energy homeostasis in the body is a highly complex process that requires extensive research. Neuroscience researchers have discovered that special hypothalamic nuclei, as well as brain neurotransmitters and neuromodulators, play an important role in the central control of nutritional behaviors [7-15].

Hypothalamus exerts its controlling role through its special nuclei. These nuclei include ARC (first-order neuron), VMH, PVN, LHA, and DMH (second-order neurons) [16-18]. The ARC in the middle eminence is not covered by the BBB, so it has direct access to the signals of energy regulation with blood origin. This nucleus, with its two important neuronal populations (NPY and POMC), plays a very important role in the central control of food intake [19]. By receiving blood signals, the neuronal population in this nucleus sends the necessary message to change the nutritional status and neuronal activity of the second-order neuron [4]. The VMH is called the center of satiety and plays a role in energy homeostasis and body weight. It receives different signals from ARC and PVN through its receptors, modulates these messages, and sends appropriate output to ARC, PVN, and other brain regions involved in the central control of feeding [17, 20]. The PVN is the center of hunger and is the main output center of the hypothalamus. It receives multiple inputs from the ARC and subcortical regions. It then issues the appropriate response to the LHA and other brain regions [16, 21]. The most important task of LHA is to control nutrition according to the changes in the body's energy status. This nucleus receives the necessary messages to control the nutritional status of the body, especially from the ARC, PVN [18], and DMH [22, 23]. Then, by integrating these messages, it issues the appropriate stimulus response to VTA and other brain centers involved in the central control of food intake [24].

The DMH plays an important role in controlling feeding, body weight, and digestive behaviors [22, 23]. It is located in the tubular part of the hypothalamus and the area between the periventricular and lateral regions. In rodents, this nucleus is easily divided into several identifiable sub-regions [25]. The DMH contains two important neural populations, namely NPY and CART neurons, which are the most important ones in the central control of food intake [26]. The DMH receives diverse inputs and integrates them and issues the appropriate response through these two neuronal populations [27]. This nucleus has extensive connections with other hypothalamic nuclei in the central control of food intake. This nucleus receives multiple inputs from all the anterior, middle, and posterior nuclei of the hypothalamus [28]. The DMH also receives signals of blood origin through the cerebellum. The cerebellum transmits various inputs from the vagus nerve and signals of blood origin to the DMH. Therefore, through DMH, the hypothalamus is connected to other neural networks involved in the central control of nutrition, including the cerebellum-vagus nerve [29]. The DMH sends extensive nerve projections to all nuclei of the periventricular zone of the hypothalamus, such as PVN, LHA (except ARC), septum, hippocampus, and amygdala [27].

In the field of neurophysiology, several types of research have been conducted on distinct hypothalamic nuclei, and their roles have been investigated separately. The DMH has received little attention among these nuclei [23]. Therefore, considering the role of DMH in the central control of food input, we review the role of this nucleus in controlling central nutritional behavior.

Abbreviations-Cont'd

BBB: Blood-brain barrier
NPY: Neuropeptide Y
POMC: Pro-opiomelanocortin
VTA: Ventral tegmental area
CART: Cocaine- and amphetamine-regulated transcript
GALRs: Galanin receptors
GPCR: G protein-coupled receptors
PeH: Periventricular hypothalamus
ICV: Intracerebroventricular
GALP: Galanin-like peptide
L-bR: Leptin receptors
DR: Dopaminergic receptors
NPYR: NPY receptor
MCR: Melanocortin receptor
GHSR 1a: Growth hormone secretagogue receptor 1a
MBH: Mediobasal hypothalamic
AgRP: Agouti-related peptide
α-MSH: alpha-melanocyte-stimulating hormone.

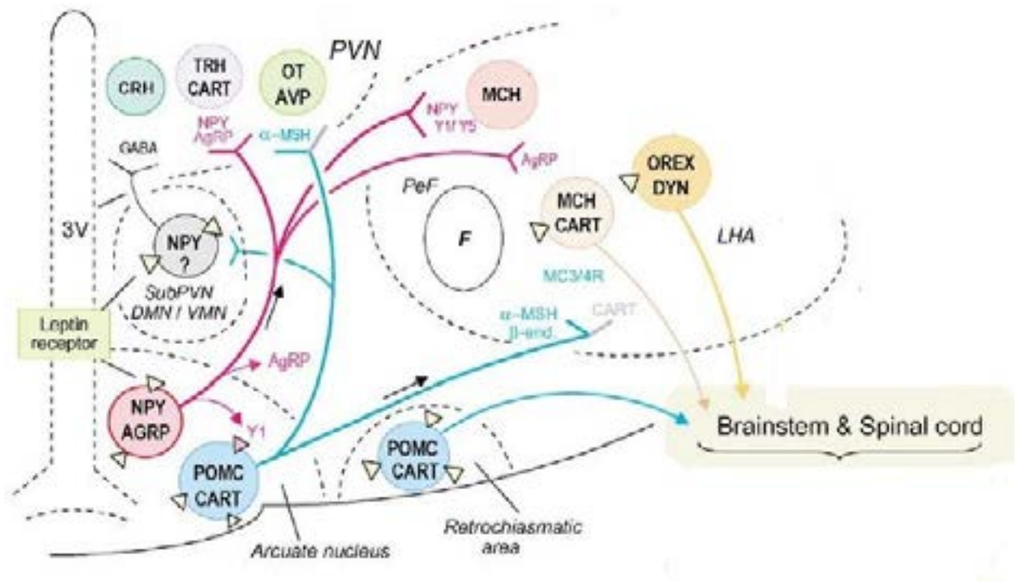

Figure 1.
Nutritional status and energy balance hypothalamic peptidergic circuitry in the rat. Receptors and communities of peptidergic neurons with their projections were defined. The middle group of hypothalamic nuclei, including the arcuate nucleus, retrochiasmatic area, dorsomedial, and ventromedial nuclei have long-form leptin receptors (ObRb, open triangles). Arcuate neuron has the mRNA of neuropeptide Y (NPY) and agouti-related protein (AgRP). These neuron populations project output to the paraventricular nucleus (PVN) and the perifornical/lateral hypothalamus (PeF). These neuron populations project output to autonomic and motor areas of the brainstem and spinal cord, PVN and DMH, and other brain areas (not shown). One neuron group that receives input from these ARC projections in the lateral hypothalamus (LHA) involves MCH, CART, orexin-A (OREX), and dynorphin (DYN). Various populations of these neurochemically special cell groups produce 'ascending' (cortex, amygdala, hippocampus, thalamus) and 'descending' projections to promotor (medullary motor nuclei), locomotor (pedunculopontine locomotor area and spinal cord), and autonomic premotor and motor areas (dorsal motor nucleus of the vagus, A5, RVLM, and ILM) (dorsal motor nucleus of the vagus, A5, RVLM, and ILM) [81].

Study design

Several reliable papers from electronic sources were used in this review article. Creditable articles indexed in the Web of Science, Scopus, PubMed, SID, Google Scholar, and ISI databases using the keywords "feeding central regulation", "hypothalamic dorsomedial nucleus", "brain neurotransmitters", and "brain neuromodulator" were surveyed.

Galanin

Galanin is a neuropeptide found in CNS, especially the hypothalamus, and exerts its effect via GALRs (Table 1). It helps regulate feeding, body weight, reproduction, and growth. The GALRs, as members of the GPCR family, are classified into three types [5, 30]. GALR1 is mostly found in the prefrontal cortex, medial thalamus, and central amygdala. GALR2 is presented in the granule cell layer of the dentate gyrus, cerebellar cortex, and mammillary bodies. GALR3 is found in the hypothalamus [31]. In mice, galanin is distributed in all special nuclei of the hypothalamus, especially VMH. In rats, galanin is most distributed in DMH and PeH [32]. Galanin stimulates eating through various brain regions, especially DMH [33]. Central administration of galanin increased food consumption in rodents. As well as, intracerebroventricular (ICV) administration of galanin stimulates feeding in various hypothalamic nuclei such as DMH in satiated rats [34]. Moreover, the ICV injection of 1 nmol galanin increased feeding in rats with free access to food and water (Table 2). Galanin causes a central increase in food intake via up-regulating c-FOS in GALR1 in DMH [31].

Galanin-like peptide

The GALP, a 60-amino acid neuropeptide, was discovered in the hypothalamus of pigs and is linked to GALRs (Table 1) [30]. GALR1 is mostly distributed in the CNS, while GALR2 and 3 were distributed to a lesser extent in the CNS and peripheral tissues [35]. GALP has a higher affinity for binding to GALR2 than other receptors and functions in the hypothalamus via GALR2 [36]. In mice, the GLAP neurons are

Table 1.
Basic receptors involved in the central control of feeding in DMH.

Receptor	Receptor Category	Receptor Location (s)	Action (s)	Action Mechanism	Ref.
GALR2	GPCR	DMH	Increased food intake	Increased c-Fos expression	[36]
DR2	GPCR	DMH	Decreased food intake	Inhibits the formation of cAMP	[48]
GHSR	GPCR	ARC, and DMH	Increased food intake	Increased c-Fos expression	[60]
Lb-R	Class 1 cytokine receptor	ARC, and DMH	Decreased food intake	Increased c-Fos expression	[79]
NPYR	GPCR	ARC, PVN, VMH, and DMH	Increased food intake	Increase in the GABA release to the POMC neuron	[74]

distributed in the ARC [37]. Leptin receptors (L-bR) are expressed in the GALP neurons. Therefore, GALP has a direct effect on food intake by communicating with leptin [30, 37]. In rats and mice, GALP seems to have different effects. In rats, this leads to a temporary rise in feeding, followed by a reduction in eating and body weight [38]. This transient increase in feeding is linked to the activation of orexin neurons in LHA and NPY neurons in DMH [36, 39]. In mice, it only reduces food intake and body weight [40]. In mice, the repeated intranasal administration of 2 nmol of GALP reduced food intake, water intake, and body weight in 24 hours [30]. Different doses of GALP have diverse effects on feeding. A low dose (1-2 nmol) reduces food intake, whereas a high dose (4 nmol) does not affect feeding. High doses may reduce receptor expression and sensitivity to GALP [41]. In another study, it has been shown that galanin ICV injection increased food intake for the initial 2 hours in rats. GALP upregulates NPY neurons in the DMH. It also raises the level of c-Fos expression in these neurons and augments food intake (Table 2) [36]. As a result, GALP in mice decreased food intake via communication with leptin neurons. In rats, GALP increased food intake via activating orexin neurons in LHA and c-FOS expression in NPY neurons.

Dopamine

Dopamine is a vital neurotransmitter in the CNS, which is produced from tyrosine amino acid [42]. Dopamine neurons are found in the hypothalamus, especially in ARC, DMH, and LHA [43]. Dopaminergic neurons in the hypothalamus communicate with GABAergic, and POMC neurons in ARC and transmit nerve projections to PVN and LHA [44]. Dopamine exerts its effects on feeding control through DRs, which are GPCR. These receptors include DR1-DR5. Dopamine affects feeding via DR1 and DR2 [45]. DR1 was found in suprachiasmatic nuclei, PVN, LHA, VMH, and DMH. DR2 was expressed in LHA, PVN, VMH, and ARC (Table 1) [43]. The impacts of dopamine on the central control of eating depend on the type of nucleus, receptor, and overall energy condition of the body [45]. As well, dopamine seems to have diverse effects on feeding in LHA and VMH [3]. In LHA, dopamine levels are high in response to feeding and during feeding. Dopamine levels in VMH increased during fasting and after feeding. DR2 was found in NPY neurons, ARC, and PVN. When dopamine binds to DR2 in NPY neurons in PVN and ARC, inhibits NPY neurons in ARC and PVN. Consequently, NPY level declines and NPY does not bind NPYRs in DMH. The NPY cannot stimulate DMH. Finally, decreased food intake in rat[43, 46]. As well, dopamine binds to DR1 in POMC neurons, stimulating it. POMC via MCR4 inhibited DMH orexigenic output. As a result, food intake is suppressed in mice via indirect effects (Table 2) [43, 46, 47]. Furthermore, DMH sends these neural projections to LHA and suppresses feeding [48]. Dopamine inhibits feeding by inhibiting NPY neurons and stimulating POMC neurons via DMH.

Ghrelin

Ghrelin is a peptide with 28 amino acids derived from the stomach and released in reaction to a change in nutritional status [49]. It is synthesized and secreted in low volumes in the brain [50]. This hormone is orexigenic and increases in response to a massive decrease in energy [51]. Ghrelin is considered a blood glucose regulator, appetite controller, and anti-depressant [52, 53]. Ghrelin neurons transmit nerve projection to hypothalamic nuclei, including ARC, PVN, VMH, and DMH [54]. Ghrelin exerts its multiple and essential functions through GHSR1a, which is a part of GPCR (Table 1) [55]. This receptor is widely expressed in the hypothalamus, especially in MBH, ARC, PVN, VMH, and DMH [56, 57]. Moreover, ghrelin projection is transmitted to extra hypothalamic regions, namely the amygdala and septum [50]. Among different hypothalamic nuclei, DMH is sensitive to the regulation of ghrelin secretion in response to feeding behaviors stimuli [58]. Peripheral and central administration of ghrelin increases feed consumption and body weight [59]. GHSR1a expresses NPY/AgRP neurons in ARC [60] and DMH [61]. It increases the activity of these neurons and upregulates NPY. The NPY neurons transmit orexigenic output to DMH. Therefore, DMH sends orexigenic output to the PVN [62]. The ICV and peripheral injection of ghrelin-induced feeding in rats that had free access to food [63, 64], and also upregulated c-Fos in NPY neurons in ARC. Furthermore, induced c-Fos expression in DMH and PVN. Following the stimulation of NPY neurons in ARC, this nucleus sends excitatory projections to DMH, stimulating it. With DMH activation orexigenic output is sent to PVN [65]. Therefore, via this pathway, DMH exerts its orexigenic effect on feeding in rats (Table 2) [66]. Ghrelin also affects nutrition by reducing signaling from dopamine and serotonin [67]. In the brain, ghrelin neurons interact with dopaminergic neurons, and dopamine modulates an increased effect of ghrelin in nutritional behavior [68]. In addition, ghrelin reduces serotonin release to synaptic cleft [69]. Ghrelin raises NPY activity in ARC and DMH via binding to GHSR1a. In addition to directly increasing the level of NPY in the DMH, the level of this neuropeptide is increased in the ARC and sends excitatory input to the DMH. Next, DMH sends orexigenic messages to PVN.

Neuropeptide Y

The NPY is a vital and strong orexigenic compound in CNS and is synthesized in ARC and DMH. DMH contains NPYR [61]. NPY is a 36-amino acid peptide, which is a member of the pancreatic polypeptide family. NPY is distributed in CNS, especially the hypothalamus [7], and plays an orexigenic role with NPYR. The NPYR belongs to the GPCR family. NPY has multiple receptors, including NPYR1, NPYR2, NPYR4, and NPYR5. The DMH contains NPY1R and NPY5R (Table 1) [70]. NPY exerts orexigenic effects via these receptors. The NPY neurons in DMH are considered gabaergic and non-sensitive neurons to leptin [71]. NPY levels in DMH increase in response to food deprivation and stimulate this nucleus. Now, this nucleus transmits orexigenic output to other nuclei [61]. In mice, NPY neurons in DMH are involved in central feeding regulation [72, 73]. It has been shown that POMC neurons in ARC may have an inhibitory role on NPY neurons in DMH. The POMC-GABAergic neurons in ARC send inhibitory output to DMH. In DMH, MCR4 is expressed. The POMC neuron via MCR4 exerts an inhibitory effect on NPY neurons [1]. During starvation in rats, NPY levels are increased in

Table 2.
The role of main neurotransmitters in the central control of feeding in the DMH.

Substance Type	Animal Type	Administration Type	Co-transmitter	First Order Neuron	Second Order Neuron	Function (s)	Other Central/Peripheral Action (s)	Action Mechanism (s)	Dosage of the drug (s)	Ref.
GALP	Mice	Intranasal	NPY	ARC	DMH, LHA	Decreased feeding	Decreased water intake, and body weight	Interleukin-1 receptor	2 nmol	[30]
GALP	Rat	ICV	NPY	VMH	PVN	Increased feeding	-	Increased in c-FOS expression	0.3 nmol/5µl	[36]
Sulpiride	Rat	Intra hypothalamic	Serotonin	ARC	LAH	Increased feeding	Increased water intake	cAMP level inhibited	8 µg/ 0.5 µl	[48]
Ghrelin	Rat	Intraperitoneal	NPY	ARC	DMH	Increased feeding	Increased c-Fos-like-immunoreactivity in PVN	Increased of c-Fos expression	0.3 nmol	[65]
Leptin	Rat	Intravenous	NPY	DMH	PVN	Decreased feeding	Increased energy consumption	Increased of c-Fos expression	1 mg/Kg	[76]
Angiopoietin-like protein 8	Mice	ICV	NPY	ARC	DMH	Decreased feeding	Decreased body weight	Decreased of c-Fos expression	2 µg/ml	[73]

the ARC [74] and DMH [75]. Also, the GABAergic inhibitory branch inhibits the POMC neurons in the ARC. As a result, their inhibitory effect is removed from NPY neurons in DMH. Then, NPY exerts its additive effect on food intake by sending excitatory outputs to other brain regions [72]. The main brain neurotransmitter for controlling feeding in DMH is NPY. Central injection of NPY augments feeding and body weight (Table 2) [75]. In response to starvation, the NPY level rises in both ARC and DMH. On the other hand, the inhibitory GABAergic branch of ARC inhibits POMC neurons. As a result, NPY stimulates DMH, and DMH exports the necessary orexigenic message.

Leptin

Leptin is an adipose tissue-derived hormone that inhibits ingestion and facilitates weight maintenance. Lack of leptin or reduced sensitivity to leptin causes obesity. Therefore, leptin is a vital hormone in controlling food intake. The Lb-R, which is found throughout CNS, is a member of the class 1 cytokine receptor family (Table 1) [18]. Leptin is highly expressed in the hypothalamus particularly ARC, VMH, and DMH [71]. Leptin has a receptor on GABAergic neurons in DMH. Therefore, leptin inhibits GABAergic neurons via Lb-R and restrains projection transmitted to PVN. Leptin reduces feeding in rats via this pathway [76, 77]. Furthermore, leptin suppresses feeding and promotes energy consumption by activating other neuron populations [78]. Leptin exerts its effect on nutritional behavior via increased c-Fos expression in ARC, DMH, and PVN [79]. The NPY neurons in ARC transmitted nerve projection to DMH. The main site of leptin action is the hypothalamus. It has been shown that the ICV injection of leptin reduces digestion by affecting the hypothalamus (Table 2). Furthermore, circulating leptin enters CNS through MBH, and then exerts its effect on food intake by transmitting nerve projections from ARC to DMH, and then to PVN. Finally, feeding is reduced. Leptin inhibits the expression of NPY mRNA and increases the level of α-MSH in the hypothalamus. It also reduces the level of this neurotransmitter in ARC, DMH, and PVN. Neurons expressing Lb-R in DMH play a key and essential role in feeding control [80]. Leptin inhibits GABAergic neurons in DMH through Lb-R. It also down-regulates NPY and up-regulates α-MSH in ARC and DMH. As a result, through these pathways, the increasing effects of DMH on food intake are inhibited, and it reduces food intake.

Conclusion

DMH plays an important role in the central control of feeding, but it has received very little attention. NPY in this nucleus plays a critical role in the central stimulation of food intake. Galanin and GALP stimulate central feeding behavior via their receptors in this nucleus. The effect of dopamine on the central control of food intake appears to be highly dependent on the nutritional level, receptor type, and nucleus involved. Dopamine inhibits NPY neurons and stimulates POMC neurons via dopaminergic receptors, resulting in a central decrease in digestion. Ghrelin also increases central food intake by raising NPY levels. Leptin reduces central food intake by decreasing NPY levels (graphical abstract).

Future directions

Considering the effect of DMH on the central control of nutritional behavior, the authors recommend that future research be conducted on the effect of other neurotransmitters on the central control of feed intake via this nucleus.

Funding

This review article did not receive any specific grant from funding agencies in the public, commercial, and not-for-profit sectors.

Statement of Human and Animal Rights

This study has not been performed on any humans or animals.

Authors' Contributions

Farshid Hamidi, and Shiba yousefvand. Farshid Hamidi presented the main idea and plan. Farshid Hamidi and Shiba yousefvand conducted scientific searches. Farshid Hamidi and Shiba yousefvand performed collecting and analyzing information and articles. Shiba Yousefvand wrote the paper. Farshid Hamidi reviewed the paper. Farshid Hamidi and Shiba yousefvand drew an abstract graphical design.

Acknowledgements

The authors thank the Ferdowsi University of Mashhad for their cooperation.

Competing Interests

The authors do not have conflict of interest.

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How to cite this article
Yousefvand Sh , Hamidi F. Role of Various Neurotransmitters in the Central Regulation of Food Intake in the Dorsomedial Nucleus of the Hypothalamus. Iran J Vet Sci Technol. 2023; 15(2): 1-10.
DOI: https://doi.org/10.22067/ijvst.2023.79476.1203
URL:https://ijvst.um.ac.ir/article_43830.html